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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/030,188	02/04/2002	John Walter Liebeschuetz	00217/US	8359

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EXAMINER	
PATEL, SUDHAKER B	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 10/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/030,188	LIEBESCHUETZ ET AL.	
	Examiner	Art Unit	
	Sudhaker B. Patel, D.Sc.Tech.	1624	

-- The MAILING DATE of this communication app ars on th cover sh t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 September 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15,17,18,21-26,29 and 32-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15,17,18,21-26,29 and 32-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☒ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of invention of Group I wherein Y is CR1b, Cy is a phenyl, naphthyl or a homocyclic, and also election of a species of species of Example 13(= 4-[(indole-6-carbonyl-D-phenylglycineyl) aminomethyl]-1-cyclopentyl piperidine) as recited in page 97 of the specification in Paper No. 6 dated 9/1/3/03 is acknowledged. Applicants have cancelled claims 16,19,20,27,28,30,31, added new claim 36, and amended claims 1,2,18,23,32,33,34. Therefore, the claims in this application are the claims 1-15,17,18,21-26,29,32-36.

The election/restriction is considered proper and is now made FINAL.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on 7/7/03 as paper # 4. is being considered by the examiner. Signed copy of PTO Form 1449 is enclosed with this communication for applicants' record

Priority

3. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copies of PCT/GB 00/02302 filed 6/13/2000 & UK Sr. No. 0030305.7 filed 12/13/2000. have been received in parent WIPO Application. No. PCT GB 01/02551 filed 6/12/2001. for priority papers as submitted to WIPO for PCT/GB 00/02302 filed 6/13/2000 & UK Sr. No. 0030305.7 filed 12/13/2000. The priority date of 6/12/2001 can be granted for instant application, and not a priority date 6/13/2000 which is filing date of PCT/GB00/02302 for the reasons stated bellow.

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims1-15, 17,18,21-26,29,32-36 provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims of copending Application No. 09926712 filed 12/6/2001, and claiming priority to U.S. Provisional Application No. 60/142064 filed 2/7/1999. Although the conflicting claims are not identical, they are not patentably distinct from each other because the compounds, composition and method of use as recited by the ref. '712, claims 1,2,4,5,6,7,10,11,16,19,23,29,38,41 Formula (I): R2-X-X-Y (Cy)-L-Lp (D) n over lap with instant claims1-15, 17,18,21-26,29,32-36. Instant claim 1 Formula (I) is: R2-X-X-Y (Cy)-L-Lp (D) n, and the variables have same meanings as the ref. '712.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-15,17,18,21-26,29,32-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Following reasons apply.

8. Claims 1, 2,29 recite X component as C, N etc. In the bridge –X-X- only 2 valences are satisfied for both of C & N atoms. Therefore, the rest of the valence is left open for any and all kinds of various groups which could be either H atom(s) or else. Correction is required.

9. Claims 1,2,29 recite Cy component as "Homocycle". Specification and claims do not exactly define what is included as well as what in excluded in the meanings of this term.

10. Claims 1,2,29 recite various components as" optionally substituted". This term does not exactly define the number of substituents, exact connection of these substitutents to which carbon atom(s) in a bridge or a ring,

11. Claims 1,2,29 recite L component which is presented as:" An organic linker group containing 1-5 backbone atoms selected from C, N, O, and S, or a branched alkyl or cyclic group". This definition is unclear. What does it have other than the backbone atoms? Also, what are the exact definitions of branched alkyl and cyclic group? Does cyclic group include any and all rings?

12. Claim 1 is related to a serine protease inhibitor, but the component of the generic Formula " R2-X-X-Y (Cy)-L-Lp (D) n are defined as optionally substituted in various position with "and/or" terms. This is not acceptable because it includes a mixture of

compounds as well, and not a single compound at any time as claimed. Also, See Ex parte Anderegg, 51 USPQ 66.

Claim Rejections - 35 USC § 112

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claim 29 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for use as an anticoagulant, does not reasonably provide enablement for treatment of a human or non-human animal body to combat any and all thrombotic disorder(s). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

15. Specification in pages 1-3 describes use of serine protease inhibitors in addition to treatment of thrombotic diseases, a wide variety of other areas such as oncology, neurology, haematology, pulmonary medicine, immunology, inflammation and infectious diseases. Also, in page 2 lines 1-5 define the "thrombotic diseases" as asthma, emphysema, cirrhosis, arthritis, carcinoma, melanoma, restenosis, atheroma, trauma, shock, reperfusion injury, and use of instant compounds as a part of combination therapy an anticoagulant or with a throbolytic agent (see page 2 lines 33-34).

16. In cases directed to chemical compounds, which are being used for their physiological/biological activity, the scope of the claims must have a reasonable correlation to the scope of enablement provided by the specification. See in re Surrey 151 USPQ 724 regarding sufficiency of disclosure for a Markush group and In re Wiggins 179 USPQ 421.

17. Compounds and physiologically-tolerable salts thereof as recited in the claims read on all such moieties regardless of complexity of structure and point of attachment to the heterocyclic core for which there is no sufficient teaching how to make and how to use at any one selective location among the many possible sites present. The situation is more confusing when a skilled person in the art tries to visualize the multiple possibilities of combining a compound of claim 1(or claims dependent on it) and/ or its composition in its physiologically-tolerable salt(s) form in combination with other agents. Applicants provide no reasonable assurance that any and all derivatives of the instant compounds and their combinations either alone or in a combination package for pharmaceutical treatment as outlined above, will have ability to generate the compounds in vivo by one or more processes.

18. In evaluating the enablement question, several factors are to be considered. In re Wands, 8 USPQ 2d 1400 (Fed. Cir. 1988); Ex parte Forman, 230 USPQ 546. The factors include:***(1).*** The nature of invention;***(2).*** the state of prior art ;***(3).*** the predictability or lack thereof in the art;***(4).*** the amount of direction or guidance present;***(5).*** the presence or absence of working examples;***(6).*** the breadth of the claims, and ***(7).*** the quantity of experimentation needed.

The claims are drawn to compounds, their physiologically-tolerable salt(s) either alone or in combination with other pharmaceuticals, and method(s) (but not limited to) of treating thrombotic disorders in a human or non-human body.

1). The nature of the invention: The compounds and method of use claim(s) are drawn in part to method of treatment of any and all kinds of disorders related to serine protease factor Xa activity.
2). The state of prior art: There are no known compounds of similar structure which have been demonstrated to treating a human or non-human body comprising administering an effective amount of a compound or its physiologaclly-tolerable salt of generic claim 1.
3). The predictability or lack thereof in the art: It is presumed in the treatment of mammal suffering from a physiological condition(s) related to serine protease inhibitor as claimed herein, there is a way of identifying those humans and non-humans who may develop any kind of physiological conditions including (but not limited to) a single disorder. There is no evidence of record, which would enable the skilled artisan in the identification of the subjects who have the potential of becoming afflicted with the physiological disorders as claimed herein.
4). The amount of direction or guidance present and **5).** The presence or absence of working examples: There are no doses present to direct one to protect a potential host from the multiples of physiologically related disorders(s) of various types.
6). The breadth of the claims: The claims are drawn to physiological conditions (not limited to a single disorder and whose treatment(s) is unknown.
7). The quantity of experimentation need would be and undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan for the many reasons stated above.

References to show the state of art related to activity of serine protease inhibitors:

- **Neutrophile serine proteinases and PARs:**

Uehara et al (Pubmed Abstract 12759451, also cited as J. Immunol., 170/11,5690-6(2003)) state that:" These findings suggest that neutrophile serine proteinases have equal ability to activate human nonepithelial cells through PAR-2 to produce inflammatory cytokines and may control a number of inflammatory processes such as periodontitis".

- **MCP-1 and venous thrombi:**

Humphries et al(PubMed Abstract 10550187, also cited as J. Vasc. Surg., 30/5,894-9(1999)) state that:" Venous thrombus MCP-1 levels increase during normal

resolution. MCP-1 treatment increased the organization and resolution of thrombi. MCP-1 may therefore be of therapeutic use".

- **Recurrent venous thrombosis and markers of inflammation:**

van Aken et al(PubMed Abstract 10780312, also cited as Thromb Haemost. 83/4, 536-9(2000)) state that:" This is the first clinical stage showing that an increase in inflammatory mediators is associated with venous thrombosis. Future prospective studies are necessary to clarify the casual nature of the inflammatory process with respect to venous thrombosis".

- **Current drug treatment strategies for disseminated intravascular coagulation:**

de Jonge et al(PubMed Abstract 9617592, also cited as Drugs, 55/6,767-77(1998)) state that:"Results of studies on protein C concentrate, thrombomodulin or inhibitors of tissue factor are promising, but the efficacy and safety of these novel strategies remains to be established in appropriate clinical trial".

Thus, factors such as "sufficient working examples", "the level of skilled in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims.

In view of the extreme difficulties that have been and are still being encountered in the treatment of as asthma, emphysema, cirrhosis, arthritis, carcinoma, melanoma,restenosis, atheroma, trauma, shock, reperfusion injury, such utilities are unbelievable on their face and therefore they must be supported by sufficient evidence demonstrating such utilities.

Pages 163-8 describe various prior arts describing uses of various compounds, which display inhibitory effects on serine proteases such as factor Xa, thrombin etc., but specifically fail to provide any pertinent data related to instant compounds for the reader (examiner) to visualize the utility.

Lines 21-22 in page 164 state that:" Compounds of the invention were found to have activity in these assays (= factorXa, trypsin, thrombin, plasmin and urokinase)". Lines 29-30 in page168 state that:" Compounds of the invention were found to be potent inhibitors of factor Xa". These data does not serve the purpose of treating human and nonhuman body without further experimentation. These assays do serve as screening test, but isn't designed to demonstrate "practical utility". It is designed to determine which compounds ought to be tested for actual utility.

See Brenner v. Manson, 148 USPQ 689 which requires that utility be developed up to a point where "specific benefits exist in currently available form". The tests and assays as provided by the applicants cannot possibly meet such a standard. Note Bindra v.s.. Kelly 206 USPQ 570, where, if "actual testing" is not done (and here, it is not) then one must establish "such facts as would be convincing that such utility could be foretold with certainty".

Despite intensive efforts, pharmaceutical science has been unable to find a way of getting a single compound for a method of treating of all thrombotic disorders

including diseases yet to be discovered as claimed herein simultaneously. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has been accomplished, *In re Ferens*, 163 USPQ 609. No such evidence has been presented in this case. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ 2nd.

Conclusion

Allowable Subject Matter

19. Claims related to compounds and pharmaceutical composition would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

20. The following is a statement of reasons for the indication of allowable subject matter: The closest prior art of record reference Kerwin et al (U.S.P. 5346907) teaches Amino Acid Analog CCK Antagonists with a core: " Heterocycle-NH-CO-N (R1)-CH (R2)-CO-NR3R4, wherein R3/R4 can form a piperidine ring".

21. The ref. '907 does not indicate or suggest to arrive at instant compounds with a core:" Heterocycle-CO-NH-CH (Phenyl/Aryl)-CO-NH-Aklylene-piperidine-cyclopentane".

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sudhaker B. Patel, D.Sc.Tech. whose telephone number is 703 308 4709. The examiner can normally be reached on 6:30 to 5:00 pm (Monday-Thursday).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mukund J. Shah can be reached on 703 308 4716 or Sr. Examiner Mr. Richard Raymond at (703) 308 4523.

The fax phone numbers for the organization where this application or proceeding is assigned are 703 308 4556 for regular communications and 703 308 4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308 1235.

MARK L. BERCH
PRIMARY EXAMINER
GROUP 120 - ART UNIT 122

Sudhaker B.Patel, D.Sc.Tech.
October 8, 2003.